Antepartum Evaluation of the High-Risk Fetus: Problems and Prospects

by S. Fabro*

The chief obstetrical problems encountered today in the prenatal evaluation of the high-risk fetus are presented.

Advantages and pitfalls of recent techniques utilized in the management of the high-risk pregnancy are discussed. They include: a prenatal scoring system for identifying the high-risk population; examination of the karyotype of cells in amniotic fluid, and quantitation of a-fetoprotein levels in maternal plasma and amniotic fluid for the early prenatal detection of birth defects; ultrasonography for the intrauterine diagnosis of fetal growth retardation and assessment of fetal maturity; the use of maternal urinary estriol excretion, maternal plasma human placental lactogen levels and the oxytocin stress test for the early detection of fetal distress; estimation of fetal maturity by amniotic fluid analysis of lecithin or lecithin-sphingomyelin ratios, creatinine and Blue Nile fetal cell staining.

Newer, still experimental, techniques (e.g., fetal breathing movements, fetoscopy, and dehydroepiandrosterone plasma clearance) are viewed in light of further possible decreases in maternal and perinatal mortality.

Maternal mortality in the U.S. showed a dramatic decrease, approximately 10-fold, between 1930 and 1960. This decrease has made it possible to sharpen our focus on the developing fetus, since over the same period of time, and with the same high standards of medical care, fetal death and infant mortality has declined much less dramatically (1).

One of the reasons for the lack of improvement in neonatal survival is probably that the human being *in utero* is relatively inaccessible to physiologic and/or biochemical measurements. Thus, our knowledge about the intrauterine development of the human conceptus is scanty and indirect; it is mainly derived from animal experiments or from retrospective analyses of clinical material.

By the latter method it has been possible to identify the prenatal factors which are most likely to be associated with poor fetal outcome. These factors include a history of medical or obstetrical problems, low socioeconomic status, and the development of medical complications during the gestational period (2). Quantitative methods of scoring a pregnancy for its potential high risk are currently gaining acceptance. The clinical utility of a numerical scoring system is validated by the fact that pregnancies with high prenatal risk scores are associated with increased perinatal mortality and morbidity (3,4).

In evaluating the risk encountered with each pregnancy, obstetricians try to answer the following five questions: (1) Is the fetus malformed? (2) Is the fetus growing normally? (3) Is the fetus in distress? (4) How much "reserve" does the fetus have? and (5) Is the fetus capable of extrauterine life?

Congenital malformations occur in 3-4% of births, and they are responsible for nearly 15% of all infant mortality (5).

*Columbia Hospital for Women, Division of Pharmacology and Environmental Toxicology, The George Washington University, Departments of Obstetrics and Gynecology and Pharmacology, Washington, D.C. 20037.

Until recently, it was impossible for the obstetrician to determine whether a fetus was malformed, and the diagnosis a congenital anomaly was usually made at birth. The first breakthrough in the prenatal diagnosis of congenital malformations came in 1954, when Steele and Breg showed that fetuses with chromosomal defects can be identified in high-risk patients by culturing and karyotyping fetal cells obtained by amniocentesis (6). For this purpose, amniocentesis is carried out early in pregnancy, at 14-16 weeks of gestation, in patients who are suspected of carrying a fetus with chromosomal aberrations. If the fetus is found to have a significantly abnormal karyotype, interruption of pregnancy can be performed before the fetus attains viability. The early prenatal diagnosis of genetically determined errors of metabolism, e.g., Tay-Sachs disease, Niemann-Pick disease, has also become possible.

Table 1 shows a summary of 800 consecutive cases for which prenatal chromosome analysis was requested (7). Maternal age of 35 years or older, and a previous child with Down's syndrome were the two most common reasons for performing amniocentesis. Of the 800 fetuses, 27 (3.4%) possessed genetic defects, an incidence approximately 6-7 times that in the general population. The outcome of pregnancy in 648 of these cases was as follows: therapeutic abortion of 18 of the fetuses with chromosomal aberrations was performed; five patients terminated their pregnancies by voluntary abortion; 22 aborted spontaneously; and there were 6 stillbirths. However,

Table 1. Analysis of consecutive experience with 800 cases for prenatal genetic diagnosis.[a]

Indication for amniocentesis	No.	"Affected" fetuses
Translocation carrier	11	3[b]
Maternal age 35-39	218	2[c]
Maternal age 40 +	195	5[d]
Previous Down's syndrome	120	0
Family history of Down's syndrome	48	1[b]
Previous neural tube defect	35	0
Miscellaneous	116	1[e]
X-Linked disorders	16	8
Metabolic disorders	41	7[f]

[a] Data of Milunsky (7).
[b] Unbalanced D/G translocation (3).
[c] 47,XXY (2).
[d] Trisomy 18 (2), trisomy 21 (2), mosaicism 46,XY/47,XXY (1).
[e] Chromosomal breakage, ring chromosome (1).
[f] Tay-Sachs (3), Hunter's (1), Niemann-Pick (1); 47,XXY (2).

among the 597 live births in this series of patients, 15 (2.5%) were abnormal. The type of malformations observed were: Down's syndrome, Klinefelter's syndrome, craniosynostosis, hydrocephaly, myelomeningocoele, cleft lip (two cases), phocomelia, claw deformity, Tetralogy of Fallot, hypospadias (two cases), cystic fibrosis, adrenogenital syndrome, multiple anomalies.

Chromosomal abnormalities had been detected prenatally in the two cases with Down's and Klinefelter's syndrome, but the pregnancies were not terminated. The congenital malformations in the remaining 13 cases were not associated with chromosomal aberrations, and therefore could not be detected by chromosomal analysis.

With the recent observation that alpha-fetoprotein is significantly increased in the amniotic fluid of fetuses with anencephaly or spina bifida, the prenatal diagnosis of another group of rather frequently occurring congenital abnormalities became possible (8,9).

More recently (10), it has been shown that α-fetoprotein levels are also elevated in the serum of women 18-20 weeks pregnant who are carrying fetuses with spina bifida. This finding raises the possibility of detecting such nervous system defects by screening the pregnant population early in gestation.

However, the correlation between increases in the levels of α-fetoprotein and neural closure defects requires further investigation, since other conditions, including hydrocephaly (11), esophageal atresia (12), congenital nephrosis (13), threatened abortion (14), twin pregnancy (15), and fetal death (16) are also associated with elevated alpha-fetoprotein levels in amniotic fluid. The incidence of false positives and of false negatives must yet be defined, as must the optimal time during gestation for sampling amniotic fluid. Nevertheless, the potential promise of this approach is such that large-scale studies are clearly indicated.

The second problem of the obstetrician is to establish whether the fetus is growing normally. It is well known that two conceptuses developing in the same uterus for the same length of time (as in the case of twin pregnancies) may have different growth rates. Such situations have forced the perinatologist to define more precisely the relationship between birth weight and gestational age. As far as gestational age is concerned, newborn infants between 38 and 42 weeks of gestation are categorized as term infants; those less than 38 weeks are considered preterms, and post-term infants are those remaining *in utero*

longer than 42 weeks of gestation. Infants can also be categorized into three groups as far as birth weight is concerned: the appropriate for gestational age (AGA) are newborns whose weights fall between the 10th and 90th percentile for the normal mean growth curve; those above the 90th percentile are called "large for gestational age" (LGA); and those below the 10th percentile, the "small for gestational age" (SGA). This classification has been shown to have great prognostic value in predicting neonatal mortality. Thus, a greater incidence of mortality is found not only in infants at earlier gestational ages, but also in those infants born too small, or large, for gestational age (17).

Similarly, the IQ scores and the incidence of central nervous system handicaps in children appear to be affected by birth weight and gestational age. Thus, epilepsy, mental retardation, and cerebral palsy occurred more frequently in 8-year old children who were born prematurely or had been small for gestational age (18).

The obstetrician must evaluate the growth of the fetus in utero, but he is limited by the necessity of using noninvasive techniques for this evaluation. For the clinical estimation of gestational age, five parameters are avilable: length of amenorrhea, size of the uterus, estimated fetal body weight, "quickening," and auscultation of fetal heart by stethoscope. All of these parameters are notoriously inaccurate, and it was fortunate for the obstetrician that ultrasound scanning was introduced in clinical practice. This technique has proved invaluable not only for estimating gestational age, but also for monitoring fetal growth in utero. Thus, it has been shown that the biparietal diameter of the fetus is proportional to gestational age (19) and that the fetal biparietal diameter increases at approximately 3 mm per week from the 16th to 32nd week, after which the growth curve decreases to about 1.8 mm/week. Detection of a decrease in the growth rate of the biparietal diameter suggests that a cranial aberration is present. A reduced growth rate of the biparietal diameter has also been utilized for diagnosing intrauterine growth retardation (19). Unfortunately, this is a very insensitive method for the latter purpose, since only those infants suffering from the most severe intrauterine growth retardation show a decrease in the rate of growth of the skull. In the intrauterine-retarded fetus, one of the earliest manifestations is a decrease in the diameter of the chest followed by a decrease in its body length, and then a decreased growth rate of the skull. At the presnt time, a number of investigators are trying to develop reliable ultrasound techniques to measure the size of the fetal trunk, since a decrease in its rate of growth would provide a more sensitive method of detecting early intrauterine growth retardation (20).

However, the obstetrician must make other measurements in order to evaluate whether the fetus is in distress. One such measurement is the rate of excretion of estriol in the maternal urine. Because of the relative deficiency of 3-β-hydroxy steroid dehydrogenase in the fetal adrenals, 16-hydroxydehydroepiandrosterone sulfate is the primary compound which crosses from the fetus to the placenta. The compound is transformed by placental enzymes into estriol, which then enters the maternal circulation and is excreted in the urine, mainly as a glucuronide (21).

According to Beischer et al. (22), the mean value of urinary estriol excretion is 24 mg/24 hr, but with a large variability. Thus, values between 40 and 12 mg/24 hr are still considered normal at term.

A low urinary estriol excretion pattern has been associated with intrauterine growth retardation, whereas a consistently decreasing urinary estriol excretion rate has been associated with fetal distress (23).

There is, however, some disagreement as to the precise urinary estriol level at which fetal distress is indicated (24). Some workers consider it to be 1–3 mg in 24-hr urine, others 10–12 mg in 24-hr urine. In addition, the methodology is tricky and time-consuming, so that results sometimes may not be sufficiently accurate and/or recent to help the obstetrician in the clinical management of the patient. Numerous other conditions besides fetal distress are associated with low urinary estriol values (Table 2), which further confound the issue (21).

In order to develop better techniques for the early detection of fetal distress, several methods have so far been proposed (Table 3).

Some, such as detecting an increased rate of fetal swallowing by amniography have already been discarded. Others, such as detecting decreased fetal body and respiratory movements by electronic or ultrasound equipment, appear very promising. The diagnostic value of abnormalities in the fetal electrocardiogram is also being eveluated in the effort to develop a method for detecting fetal distress. It is hoped that one of these techniques, or a combination of them, will prove useful in diagnosing fetal distress more readily and accurately than is possible now with the methods presently available.

In managing high-risk pregnancies it is often

Table 2. Conditions associated with "low" urinary estrogen values during pregnancy.

Sample loss
    Inadequate urine collection
    Incomplete hydrolysis and/or extraction during assay
Chemical interference with methodology
    Proteins
    Glucose
    Mandelamine
    Ampicillin
    Meprobamate
    Phenolphthalein
    Senna
    Inulin
    Hexamethylenetetraamine
    Formaldehyde
    Cascara
    1,8-Dihydroxyanthraquinone
Pharmacologic action of drugs
    ACTH
    Corticosteroids
Maternal physiopathologic changes
    Fluid retention
    Decreased glomerular filtration rate
Placental enzymatic defect
    Lack of sulfatase
Fetal malformations
    Anencephaly
    Down's syndrome
    Congenital adrenal hypoplasia

Table 3. Physiological changes indicative of fetal distress.

Fetal changes	Method	Reference
Increased rate of swallowing	Amniography	(25,26)
Deceased movements	Electronic rec.	(27)
Decreased respiratory movements	Ultrasound	(28)
Decreased response to sounds	FHR changes	(29)
Temperature changes (<1.2°F)	Thermistors	(30)
Prolonged Q-S interval	EKG	(31)
Shortened pre-ejection period [a]	EKG	(32)
No FHR changes after atropine	Fetal monitor	(33)

[a] Q-Ao interval; in sheep.

important to test whether the fetus has a sufficient "reserve" of energy so that it can tolerate physiological stresses. One such test is the stress test or oxytocin challenge test, since the stress is oxytocin-induced uterine contractions.

The main indications for the stress test are high-risk pregnancies which are likely to be associated with poor placental and/or fetal conditions, and include diabetes, toxemia, chronic hypertension, and intrauterine growth retardation. Performed on an out-patient basis, the preg-

nant patient is placed in the semisupine position and abdominal transducers for the detection of uterine contractions as well as fetal heart rate are applied. The tocotransducer will make a record of the uterine contractions and the ultrasonic transducer will detect the fetal heart rate pattern. After recording a baseline value for 10 min, uterine contractions are produced by an intravenous oxytocin infusion, at increasing doses, until an adequate uterine contraction pattern with the frequency of 3 in 10 min is established. Uterine contractions result in compression of myometrial vessels and thereby cause a transient hypoxia in the fetus. If the fetus has a "good" reserve, no changes in its fetal heart rate pattern are seen. The test is said to be negative, and assumes a good, healthy fetus. If the fetus and/or the placenta are partially compromised, the transient hypoxia will be followed by late deceleration of the fetal heart which is indicative of uterine-placental insufficiency (34).

It has also been proposed that a human placental lactogen level of less than 4 µg/ml in the maternal serum at 30-42 weeks of gestation is a sign of placental insufficiency, and that such a level correlates reasonably well with immediate fetal danger (35,36). However, other findings have confused this issue. For example, human placental lactogen is decreased in threatened abortion and is elevated in a twin pregnancy. In cases of high-risk pregnancy, such as toxemia, various authors have reported normal levels (37), low levels (38), and elevated levels (39) of human placental lactogen. Because of these discrepancies, other placental function tests have recently been proposed.

They include intervillous blood flow measurements (40), DHEA-S placental clearance (41), placental biopsy (42), and radioactive selenomethionine uptake by the placenta (43). These tests are all being evaluated, but some, like placental biopsy, appear too invasive to be used clinically; others, like radioactive selenomethionine uptake, are probably too toxic to be useful.

At the present time, then, the oxytocin challenge test appears to be the most practical way to assess placental function. Although its clinical significance has to be more clearly defined, the method is not invasive and is easy to perform on an ambulatory basis.

The last and probably most important question that the obstetrician has to answer is: Is this fetus mature? Is it capable of extrauterine life? It has been noted above that any time spontaneous or induced premature labor results in a newborn which weighs less than 2500 g, there is not only

an increased mortality rate but also a higher probability of reduced IQ and various central nervous system handicaps. It is remarkable that the cause(s) of premature labor is (are) at the present time unknown. Some of the factors associated with premature labor have been defined, but in about 50% of the cases the etiology is unknown. In addition, there are several pathological conditions which force the obstetrician to induce premature labor, the most common of which is premature rupture of the membranes. This condition accounts for nearly 60% of all the cases of spontaneous and induced premature labor. Nevertheless, little, if anything, is known of the etiology of premature rupture of the membranes. In cases where early induction of labor is elective, such as in diabetes or Rh disease, it is essential to evaluate the capability of the fetus to withstand extra-uterine life prior to rupturing the membranes. Fetal maturity in an obstetrical sense was once considered to be a function of gestational age and the estimated fetal weight, but the unreliability of these two parameters has already been discussed. A number of techniques in addition to clinical methods have been devised to improve our ability to predict fetal maturity.

With the introduction of amniocentesis, it has been possible to examine the relationship between fetal maturity and concentration of various endogenous substances in the amniotic fluid. Thus, researchers have tried to establish a relationship between fetal maturity and osmolality (44), bilirubin concentration (45), creatinine concentration (46), or the number of fat cells present in amniotic fluid (47). However, with the discovery by Gluck (48) that an increased lecithin level in the amniotic fluid is a sign of lung maturity, a new approach to this problem was possible. Subsequent studies have shown that the increased concentration of lecithin in the amniotic fluid reflects the secretion of surfactant by alveolar cells. Gluck found that a lecithin/sphingomyelin (L/S) ratio of 2 or greater is associated with lung maturity. In a normal human pregnancy this ratio is attained at about 35 weeks of gestation; there is accumulating evidence which suggests that some high-risk prenatal conditions might accelerate or delay the maturation of the L/S ratio. Accelerated maturation occurs in association with both maternal conditions (e.g., toxemia and hypertension) and placental disease (e.g., circumvallate placenta or placental insufficiency). According to Gluck, premature rupture of the membranes more than 24 hr before delivery causes acceleration in the maturation of the L/S

ratio (48), although this has been refuted recently by a group of workers in Colorado (49).

Delayed maturation of the L/S ratio may be found in the smaller of chorionic twins as well as in Class A, B and C diabetes, chronic glomerulonephritis, and hydrops fetalis (48). There is an inverse relationship between the L/S ratio and the number of deaths from hyaline membrane disease. Thus, only 0.3% of the patients with L/S ratios equal to or greater than 2 had an offspring that died of hyaline membrane disease, and this incidence increases with decreasing L/S ratios (50).

In summary, we have evaluated the most common and important obstetrical problems of the modern obstetrician. Our attitude toward the welfare of the patient has changed somewhat in recent years, and particularly changed is our approach to the fetus. In the past the fetus was not asked anything. Today in evaluating any high-risk pregnancy we have learned constantly to ask the fetus, "How well are you doing?" and, "Would you prefer to be somewhere else?" (51).

There is no doubt that improvements in our techniques will make the fetus more accessible to biochemical and physiological measurement. It is hoped that these technological advances will not only lead to decreases in perinatal mortality, but also will improve the overall quality of life of our offspring.

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